Concerted and Stepwise Solvolytic Elimination and Substitution Reactions: Stereochemistry and Substituent Effects

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Abstract: Solvolysis of the *R,R* and *R,S* isomers **2a-X** and **2b-X**, respectively, (X = I, Br, OBs) in 25 vol % acetonitrile in water gives the elimination products **4, 5a,** and **5b** along with the substitution products **2a-OH, 2b-OH, 2a-NHCOMe,** and **2b-NHCOMe**. The rates of elimination (k_E) increase with increasing acidity of the β-hydrogen of the substrate as expressed by a Brønsted parameter of $\alpha = 0.08$ and 0.07 for the iodides and the bromides, respectively. In contrast, the brosylates, which give much smaller fractions of the stable alkenes, exhibit a *negative* Brønsted parameter for the elimination, $\alpha = -0.10$. This shows that the brosylates, in contrast to the halides, do not give elimination exclusively by a solvent-promoted E1cB reaction or an E2 reaction with a large component of hydron transfer in the transition state and indicates a large amount of reaction through carbocation intermediates to give stable alkenes.
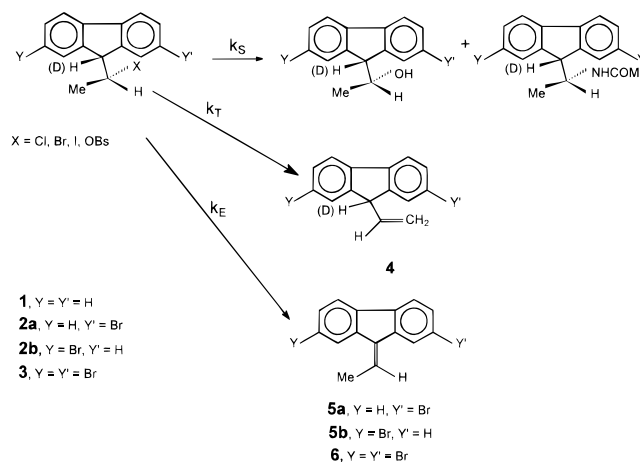
Introduction

We are interested in the factors that govern the competition between different solvolytic elimination reaction mechanisms. In this paper, we are studying competition between elimination, occuring by solvent-promoted, rate-limiting hydron-transfer from the substrate, and solvolytic elimination through a carbocationic intermediate. Concerted solvent-promoted E2 reactions have been observed recently for 9-(1-X-ethyl)fluorene (**1-X** in Scheme 1, X = Br, I) in a highly aqueous solvent.[1,2] It was concluded that the high acidity of the β-hydrogen is required for this reaction to be significant, otherwise competing stepwise solvolytic elimination and substitution reactions are predominant.[1−3] The main experimental evidence for the E2 mechanism was the measured large kinetic deuterium isotope effects and substantial Brønsted parameters of $\beta = 0.43$ and 0.41, respectively, showing that the hydron transfer is involved in the rate-limiting step. In addition, the measured small Grunwald−Winstein values indicate that the sensitivity of this reaction to the solvent ionizing power is small. However, the corresponding analogs with tosylate or brosylate leaving groups yield only a small fraction of elimination product due to the fast competing stepwise solvolytic substitution reaction.[2] Therefore, it was not possible to distinguish between several mechanistic alternatives for the elimination reactions of these esters.

We now report on a study in which we have favored the hydron-abstraction by the solvent by increasing the acidity of the substrate. This is also expected to decrease the rate of formation of products through carbocationic pathways. The results indicate that the brosylates give the stable alkenes by two competing reaction routes: stepwise via the ion pairs and concerted by hydron-abstraction by the solvent. The results also provide further support for the previously proposed concerted solvent-promoted elimination mechanism for the halides **1-Br** and **1-I**.[1,2]

This paper also includes a study of the stereochemistry of the solvent-promoted elimination reactions in addition to the stereochemistry of the substitution reactions with the solvent.

[⊗] Abstract published in *Advance ACS Abstracts,* January 1, 1997.
(1) Meng, Q.; Thibblin, A. *J. Am. Chem. Soc.* **1995,** *117,* 1839−1840.
(2) Meng, Q.; Thibblin, A. *J. Am. Chem. Soc.* **1995,** *117,* 9399−9407.
(3) Meng, Q.; Thibblin, A. *J. Chem. Soc., Chem. Commun.* **1996,** 345−346.

Scheme 1

1, Y = Y' = H
2a, Y = H, Y' = Br
2b, Y = Br, Y' = H
3, Y = Y' = Br

5a, Y = H, Y' = Br
5b, Y = Br, Y' = H
6, Y = Y' = Br

The results strongly suggest that the substitution by the solvent occurs stepwise through a carbocation intermediate by participation of the π-orbitals of the fluorene moiety in the ionization.

Results

Synthesis and Structure Assignment. The (*R,R*)-2-bromo-9-(1-X-ethyl)fluorenes **2a-X** (X = Cl, Br, I) were synthesized by treating the corresponding diastereomerically pure alcohol 2-bromo-9-(1-hydroxyethyl)fluorene (**2a-OH**) with ZnX_2−HX in chloroform. This reaction proceeded with high retention of configuration at the reaction center (>96% for **2a-Cl** and **2a-Br** and >80% for **2a-I,** *vide infra*). The smaller extent of retention of configuration for **2a-I** may be attributable to competing S_N2 reaction with I^- as nucleophile. The same procedure was used to synthesize the *R,S* isomers **2b-Cl**, **2b-Br,** and **2b-I** from the other diastereomer **2b-OH**. These reactions also showed high retention.

(*R,R*)-2-Bromo-9-(1-((4′-bromobenzenesulfonyl)oxy)ethyl)-fluorene (**2a-OBs**) was synthesized by treating the alcohol **2a-OH** and 4-bromobenzenesulfonyl chloride with pyridine in dichloromethane. This reaction should proceed with complete retention of configuration. Accordingly, only one diastereomer was obtained. The same procedure was used to prepare the *R,S* isomer **2b-OBs** from **2b-OH**.

Table 1. Rate Constants (Defined in Scheme 1) for the Reactions of **2a-X**, **2b-X**, and **3-X** in Acetonitrile (25 vol %) in Water at 70 °C

substrate[a]	$10^6 k_{obsd}$ (s^{-1})	$10^6 k_S$ (s^{-1})	$10^6 k_T$ (s^{-1})	$10^6 k_E$ (s^{-1})
2a-I[b]	179	1.6		177
2b-I[b]	168	1.4		166
2a-Br[b]	30.6	2.0		28.6
2a-Br[i,k]				$4.66 \times 10^{3\,h}$
2b-Br[b]	29.1	1.5		27.6
2b-Br[i,k]				$5.22 \times 10^{3\,h}$
2a-OBs[b]	590	513	10	67
2a-OBs	1618	388		1230
2a-OBs[g,i,j]				29.0^h
2b-OBs[b]	520	441	19	59
3-I[b]	298			298
3-Br[b]	50.3	1.0		49.2
3-Br[d,i]				$1.82 \times 10^{4\,h}$
3-Br[e,i]				$1.29 \times 10^{3\,h}$
3-Br[f,i]				92.0^h
3-OBs[b]	102	48.1	4.6	49.1
3-OBs[g,i]				$4.70 \times 10^{3\,h}$
3-OBs[e,i]				301^h
3-OBs[f,i]				9.32^h
3-OBs[g,i,j]				139^h
3-OBs[b,c]	29.4	11.3	1.4	16.8

[a] Substrate concentration 0.01−0.1 mM. [b] pH = 3. [c] Solvent: 40 vol % of MeCN in water. [d] Measured with acetate buffer, 0.025−0.10 M ([HOAc]/[NaOAc] = 4). [e] Measured with NCCH$_2$COO$^-$, 0.10−0.25 M. [f] Measured with CF$_3$COO$^-$, 0.10−0.60 M. [g] Measured with acetate buffer, 0.10−0.50 M ([NaOAc]/[HOAc] = 100). [h] In M^{-1} s^{-1}. [i] The ionic strength was maintained constant (0.75 M) with sodium perchlorate. [j] T = 35 °C. [k] Measured with acetate buffer, 0.025−0.10 M ([NaOAc]/[HOAc] = 4).

Table 2. Kinetic Deuterium Isotope Effects for the Reactions of **2a-X**, **2b-X**, and **3-X** in Acetonitrile (25 vol %) in Water at 70 °C[a]

substrate	k_{obsd}^H/k_{obsd}^D	k_S^H/k_S^D	k_T^H/k_T^D	k_E^H/k_E^D
2a-I[b]	4.6 ± 0.2	1.18 ± 0.08		4.7 ± 0.2
2b-I[b]	4.5 ± 0.2	1.18 ± 0.08		4.6 ± 0.2
2a-Br[b]	3.6 ± 0.2	1.02 ± 0.05		4.4 ± 0.2
2b-Br[b]	3.7 ± 0.2	1.02 ± 0.05		4.3 ± 0.2
2a-OBs[b]	1.07 ± 0.08	0.99 ± 0.05	0.92 ± 0.08	3.0 ± 0.1
2b-OBs[b]	1.06 ± 0.08	0.99 ± 0.05	0.95 ± 0.05	2.8 ± 0.1
3-Br[b]	3.9 ± 0.2			4.1 ± 0.2
3-Br[d,f]				4.4 ± 0.2
3-OBs[b]	1.7 ± 0.1	1.17 ± 0.08	0.93 ± 0.08	3.3 ± 0.1
3-OBs[e,f]				4.2 ± 0.2
3-OBs[b,c]	1.8 ± 0.1	1.16 ± 0.08	1.02 ± 0.05	3.4 ± 0.1

[a] The rate constants are defined in Scheme 1. [b] pH = 3. [c] MeCN (40 vol %) in water. [d] Measured with acetate buffer, 0.025−0.10 M ([HOAc]/[NaOAc] = 4). [e] Measured with acetate buffer, 0.10−0.30 M ([NaOAc]/[HOAc] = 100). [f] The ionic strength was maintained constant (0.75 M) with sodium perchlorate.

The reactions of all of the *R,R* isomers with sodium hydroxide in 25 vol % acetonitrile in water yield about 90% of alkene **5a** (Scheme 1 and Table 3), and the *R,S* isomer yields about 90% of the alkene **5b**. The structural assignments are based on these results since it is most reasonable to assume that *anti* elimination is the preferred stereochemical route with strong bases.

Strong support for these assignments was also obtained by an independent method. Thus, the stereochemical assignments of the alcohols **2a-OH** and **2b-OH** were also achieved by a combination of NMR and molecular calculation techniques (see the Experimental Section).

The ether, (*R,R*)-2-bromo-9-(1-methoxyethyl)fluorene (**2a-OMe**), and the corresponding *R,S* isomer were prepared from the appropriate alcohols by reaction with iodomethane using silver oxide as catalyst. These reactions are expected to proceed with complete retention of configuration.

Kinetics and Product Studies. The solvolysis of (*R,R*)- or (*R,S*)-2-bromo-9-(1-X-ethyl)fluorenes **2a-X** and **2b-X** (X = Cl, Br, I, OBs) in 25 vol % acetonitrile in water at 70 °C yields the

Table 3. Stereochemistry of the Elimination Reactions of **2a-X** and **2b-X** in Acetonitrile (25 vol %) in Water

	anti elimination (%)				
	base				
substrate[a]	HO$^-$ [b] (0.075 M)	solvent[c]	HMTA[d,e] (0.55 M)	HMTA[d,f] (0.29 M)	NaOAc[g] (0.75 M)
2a-I		93		93	
2a-I-d		89			
2b-I	93	92	92^c	96	93
2b-I-d		88			
2a-Br	94	75	88	80	
2b-Br	92	75	93	80	
2a-Cl	91	75 (71^c)	32		90
2b-Cl	92	79 (74^c)	40		83
2a-OBs	86	70	79^c	67	
2a-OBs-d			84^c		
2b-OBs		78			
2b-OBs-d	90		83^c		

[a] Substrate concentration 0.01−0.1 mM. [b] NaOH, at 25 °C. [c] At 70 °C. [d] Hexamethylenetetramine. [e] At 25 °C, buffer ratio [base]/[baseH$^+$] = 5.5. [f] In methanol at 25 °C, buffer ratio [base]/[baseH$^+$] = 7.6. [g] Buffer ratio [AcO$^-$]/[HOAc] = 100, at 70 °C.
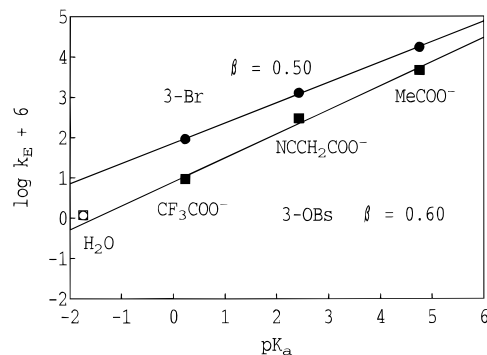
Figure 1. Brønsted plots for the elimination reactions of **3-Br** (circles) and **3-OBs** (squares) in 25 vol % of acetonitrile in water at 70 °C; ionic strength 0.75 M, maintained with sodium perchlorate.

alkenes 2-bromo-9-vinylfluorene (**4**) and *trans*- and *cis*-2-bromo-9-ethylidenefluorene (**5a** and **5b**) and the substitution products 2-bromo-9-(1-hydroxyethyl)fluorene (**2a-OH** and **2b-OH**) and 2-bromo-9-(1-acetamidoethyl)fluorene (**2a-NHCOMe** and **2b-NHCOMe**). Solvolysis in mixtures of water with methanol affords 2-bromo-9-(1-methoxyethyl)fluorene (**2a-OMe** and **2b-OMe**) instead of the amides. The solvolysis of 2,7-dibromo-9-(1-X-ethyl)fluorenes **3-X** (X = I, Br, OBs) yields similar products (Scheme 1). The kinetics of the reactions were studied by a sampling high-performance liquid chromatography procedure. The product compositions are strongly dependent on the nature of the leaving group: the halides provide predominantly the alkenes but the brosylates yield mainly the solvent substitution products (Table 1). The rate constants and reaction conditions are shown in Table 1. The measured kinetic deuterium isotope effects for the corresponding deuteriated compounds 2-bromo-(9-^{2}H)-9-(1-X-ethyl)fluorene and 2,7-dibromo-(9-^{2}H)-9-(1-X-ethyl)fluorene are collected in Table 2.

The terminal alkenes **4** are stable under the reaction conditions. For example, the ratio of **4**:(**5a** +**5b**) did not change after several half-lives of the solvolysis reactions. The amounts of *anti* elimination for reactions of **2a-X** and **2b-X** with different bases, which were measured by GC, are collected in Table 3. Brønsted plots for the general base-catalyzed formation of the stable alkene from **3-Br** and **3-OBs** with substituted acetate anions are shown in Figure 1. The slopes of these plots are β = 0.50 and 0.60, respectively.

The diastereomeric product ratios of the substitution reactions with solvent and added strong nucleophile in 40 vol % acetonitrile in water or in 60 vol % methanol in water were

Table 4. Stereochemistry of the Substitution Reactions of **2a-X-***d* and **2b-X-***d* at 90 °C

substrate	solvent[a] (vol %)	nucleophile	inversion (%)
2a-I-*d*	MeCN (40)	SCN⁻	98[b]
2b-I-*d*	MeCN (40)	SCN⁻	94[b]
2a-Br-*d*	MeCN (40)	H_2O	29
2b-Br-*d*	MeCN (40)	H_2O	41
2b-Br-*d*	MeCN (40)	SCN⁻	94[b]
2a-OBs-*d*	MeCN (40)	H_2O	7
2a-OBs-*d*	MeOH (60)	H_2O	9
2a-OBs-*d*	MeOH (60)	MeOH	15
2a-OBs-*d*	MeCN (40)	SCN⁻	78[b]
2b-OBs-*d*	MeOH (60)	H_2O	13
2b-OBs-*d*	MeOH (60)	MeOH	22
2b-OBs-*d*	MeCN (40)	SCN⁻	77[b]

[a] By volume in water, in the presence of 0.001 M HClO₄. [b] Measured for the reaction mixture in the presence of 1 M sodium thiocyanate; the values refer to thiocyanate products and not the isocyanate products which are formed in very small amounts (cf., Table 5).

Table 5. Nucleophilic Selectivities Expressed as Ratios of Second-Order Rate Constants at 70 °C (cf., Eq 1)

substrate[a]	k_{MeOH}/k_{HOH}[b]	k_{MeCN}/k_{HOH}	k_{SCN}/k_{HOH}[c,d]	[RSCN]/[RNCS][c]	k_{N_3}/k_{HOH}[c,e]
2a-OBs		0.14[g]			
2a-OBs		0.24[i]			
2a-OBs-*d*	0.95	0.49[c]	16.8	6.5	97
2b-OBs-*d*	1.09	0.49[c]	26.5	8.1	104
3-OBs-*d*	1.49	0.51[c]	122	14	
3-OBs-*d*		0.34[k]			
2a-Br-*d*	1.10		425		
2b-Br-*d*	1.56		763		
1-OBs-*d*	1.00[h]	0.40[c,h]	16[h]	5.4[h]	46[h,j]
1-OBs-*d*		0.26[f]			
1-OTs-*d*	0.98[h]	0.40[c,h]			23[h,j]
1-Br-*d*	1.02[h]	0.39[c,h]	69[h]	40[h]	~450[h]
1-Br-*d*		0.23[f]			
1-I-*d*	1.16[h]	0.41[c,h]	194[h]	56[h]	~1538[h]

[a] Substrate concentration 0.01−0.1 mM. [b] Methanol (50 vol %) in water. [c] MeCN (25 vol %) in water. [d] Using 0.75 M NaSCN. [e] Using 0.614 M NaN₃ ([N₃⁻]/[HN₃] = 10). [f] MeCN (65 vol %) in water. [g] MeCN (75 vol %) in water. [h] From ref. 2. [i] MeCN (50 vol %) in water. [j] Measured with nondeuteriated substrate. [k] MeCN (40 vol %) in water.

determined by ¹H NMR. The deuteriated substrates **2a-X-***d* and **2b-X-***d* were used in these experiments to keep the competing elimination to a minimum. The results are collected in Table 4.

The nucleophilic selectivities measured with different solvent mixtures and nucleophiles are given in Table 5. They were calculated from the measured product ratios with HPLC by using eq 1.

$$k_{Nu}/k_{HOH} = ([\textbf{2a-Nu}] + [\textbf{2b-Nu}])/([\textbf{2a-OH}] + [\textbf{2b-OH}])([H_2O]/[Nu^-]) \quad (1)$$

The parameters k_{Nu}/k_{HOH}, k_{MeCN}/k_{HOH}, and k_{MeOH}/k_{HOH} are thus dimensionless ratios of second-order rate constants. The reactions of **2a-X** or **2b-X** usually give both diastereomeric products. However, they cannot be separated by HPLC. Therefore, the sums of the two diastereomers are used.

Discussion

Solvent- and Base-Promoted E2 Reactions. The solvolytic elimination reactions of **1-I** and **1-Br** in 25 vol % acetonitrile in water to give the thermodynamically more stable alkene have been reported to be of a one-step solvent-promoted E2 type. The mechanistic assignment is based on the measured large kinetic deuterium isotope effects, Brønsted parameters for catalysis by general bases of $\beta = 0.43$ and 0.41, respectively,
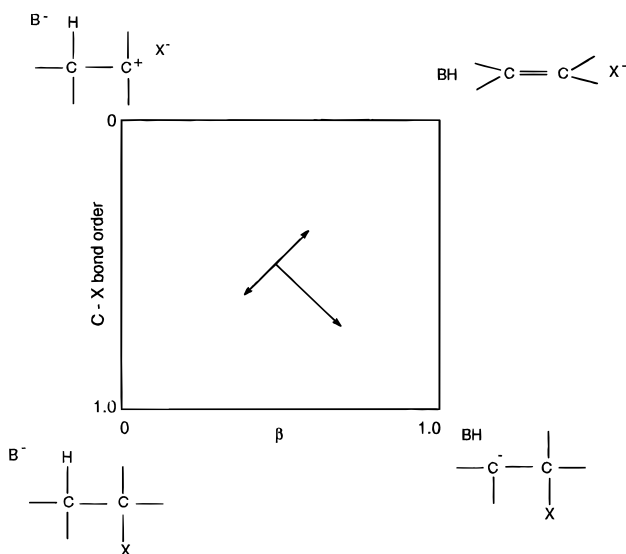
and the low sensitivities to solvent polarity.[1,2] The conclusion that the mechanism of these solvent- and base-promoted eliminations is of the E2 type, and not of the irreversible E1cB type, is inferred by comparison with the base-promoted elimination of 9-(chloromethyl)fluorene, which has been concluded to be of the E2 type.[4] The latter assignment was based on analysis of Brønsted β as a function of substrate acidity, leaving group, and α-substituents by the variable E2 transition-state theory. The solvolytic dehydrohalogenations of the more acidic substrates **2a-X**, **2b-X**, and **3-X** (X = Br, I) which give the stable alkenes **5a**, **5b**, and **6**, respectively, since the main products show similar behavior:

(i) The large isotope effects of k_{obsd}^H/k_{obsd}^D for these reactions without added base at 70 °C (Table 2) show that the reaction giving the stable alkenes does not have an irreversibly formed carbocationic intermediate in common with the other reactions, since an isotope effect of $k^H/k^D \leq 1.15$ at 25 °C is expected for the latter mechanism.[5] A reversibly formed intermediate which undergoes rate-limiting hydron transfer can be ruled out since it is unreasonable that such a short-lived ion pair would react exclusively to yield the stable alkene at low concentrations of hydroxide anion. Accordingly, the results strongly indicate a separate reaction for formation of the thermodynamically more stable alkene.

(ii) Another independent, strong indication of a one-step mechanism for the elimination reactions of these substrates is the measured Brønsted parameter for general base catalysis of $\beta = 0.50$ for **3-Br** and $\beta = 0.60$ for **3-OBs** (Figure 1). Very small β-values are expected for a mechanism in which a reversibly formed, very unstable carbocationic intermediate is dehydronated in the rate-limiting step.[6] Accordingly, these large values exclude reactions through ion pairs, either coupled with the substitution reactions or as separate reactions. However, the results are consistent with solvent-promoted E2 and irreversible E1cB reaction mechanisms.

More O'Ferrall−Jencks diagrams of the type shown in Figure 2 have been used frequently for mapping the characteristics of the transition state of β-elimination reactions.[4,7] The effect of an increasing acidity of the substrate is a lowering of the energy of the carbanionic intermediate in the lower right-hand corner

Figure 2. More O'Ferrall−Jencks diagram for alkene-forming elimination reaction (see text).

(4) Thibblin, A. *J. Am. Chem. Soc.* **1988**, *110*, 4582−4586.

(5) Westaway, K. C. In *Isotopes in Organic Chemistry*; Buncel, E., Lee, C. C., Eds.; Elsevier: Amsterdam, The Netherlands, 1987; Vol. 7, Chapter 5.

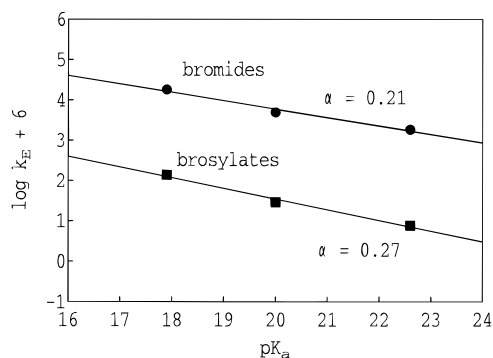(6) Thibblin, A. *Chem. Soc. Rev.* **1993**, *22*, 427−433.

Figure 3. Brønsted plots for hydron transfer from substrate to acetate anion in 25 vol % of acetonitrile in water: bromides (circles) at 70 °C and brosylates (squares) at 35 °C.
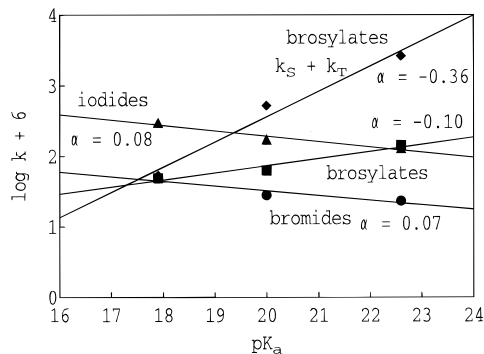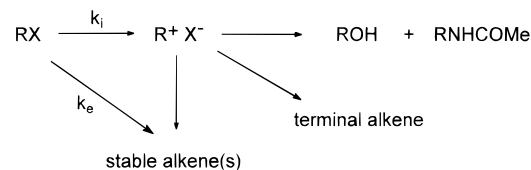

Figure 4. Brønsted plots for hydron transfer from substrate to water (k_E) and formation of stepwise solvolysis products ($k_S + k_T$), respectively, in 25 vol % of acetonitrile in water at 70 °C: iodides (triangles), bromides (circles), and brosylates (squares and diamonds).

of the diagram. This corresponds to an increase in β if the transition state of the E2 reaction is on a reaction coordinate that has a relatively large vertical component. Conversely, a large horizontal component, corresponding to proton transfer, yields a decrease in β for the E2 reaction as well as for the E1cB reaction. Thus, the increase in β with increasing acidity of the substrate, from 0.43 for **1-Br** to 0.50 for **3-Br**, suggests the E2 mechanism. The increase in Brønsted β from 0.50 for **3-Br** to 0.60 for **3-OBs** is also consistent with the E2 mechanism, since the highly polar sulfonyloxy group is expected to stabilize the carbanion corner more than the bromide leaving group.

The increase in the elimination rate constant (k_E) as a function of an increase in acidity of the substrate[8] for hydron transfer to acetate anion is shown in Figure 3. The negative slopes are in accord with base-promoted E2 and irreversible E1cB reactions. The Brønsted parameters for this general acid catalysis are relatively small: $\alpha = 0.21$ and $\alpha = 0.27$ for reactions with the bromides and brosylates, respectively. This imbalance, expressed by much smaller α- than β-values ($\beta = 0.50$ and 0.60 for **3-Br** and **3-OBs**, respectively, Figure 1) may arise from a change in bond order to carbon in the E2 transition state, for example, by a substantial amount of double-bond formation. Delocalization of negative charge into the fluorenyl ring system may also contribute to the imbalance.

Interestingly, the sensitivities to substrate acidity are considerably lower with water as base as shown in Figure 4: $\alpha = 0.08$ (iodides), $\alpha = 0.07$ (bromides), and $\alpha = -0.10$ (brosylates). The abnormal, negative value for the brosylates strongly

(7) (a) More O'Ferrall, R. A. *J. Chem. Soc. B* **1970**, 274−277. (b) Jencks, W. P. *Chem. Rev.* **1972**, *72*, 705−718. (c) Jencks, D. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 7948−7960. (d) Gandler, J. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 1937−1951.
(8) Bordwell, F. G.; McCollum, G. J. *J. Org. Chem.* **1976**, *41*, 2391−2395.

Scheme 2

indicates that these substrates react to give the stable elimination products by a different mechanism. It is not consistent with mechanisms involving exclusive rate-limiting hydron transfer from the substrates. We conclude that substantial fractions of the stable alkenes are formed from the brosylates by a stepwise carbocationic mechanism (Scheme 2). No solvent-equilibrated carbocation should be involved in these reactions owing to the very short lifetime of the intermediate (*vide infra*). The shift in the major elimination pathway from base-promoted elimination with acetate anion to stepwise carbocationic elimination (with the leaving group as the hydron abstractor) without any added base is caused by the much lower basicity of water compared to that of acetate anion. This a shift in the predominant elimination pathway can also be induced by a change in leaving group from bromide anion to brosylate anion. It reflects the much larger ionization rates of the brosylate substrates.

The corresponding unsubstituted tertiary substrate 9-(2-bromo-2-propyl)fluorene ionizes even more rapidly and only reacts in an E2 fashion in the presence of strong bases.[9,10] The shift in the major reaction pathway, from stepwise solvolysis for the tertiary substrate (which yields the less stable terminal alkene and the substitution products but only traces of the stable alkene) to solvent-promoted E2 reaction for the secondary substrate **1-Br**, is caused by the decreased reactivity of the substrate to ionization. Thus, the appearance of solvent-promoted reactions with **1-I** and **1-Br** is due to slower ionization, providing more unstable ion pairs thus making the solvent-promoted E2 reaction path competitive. The presence of bromo substituents in the 2- and 7-positions of the fluorene makes this reaction even more competitive due to the increased acidity of the β-hydron.

As discussed above, the experimental results are consistent with a competing solvent-promoted E2 reaction (k_e) and stepwise reaction (k_i) through an ion-pair intermediate (Scheme 2). Further support for this mechanistic scheme is the measured kinetic isotope effects on the observed rates of disappearance of the substrates (Table 2), which are small for the reactions of the brosylates: $k_{obsd}^H/k_{obsd}^D = 1.0$,[2] 1.1, and 1.7 for **1-OBs**, **2a-OBs**, and **3-OBs**, respectively. Accordingly, the elimination isotope effects for these substrates are relatively small, $k_E^H/k_E^D = 2.8$,[2] 3.0, and 3.3, respectively.

The isotope effect of $k_{obsd}^H/k_{obsd}^D = 1.7$ for **3-OBs** is too large for a reaction involving irreversible ionization to an ion pair (*vide supra*) but is consistent with partially reversible ionization or some contribution from competing solvent-promoted E2 elimination to give stable alkene. The increase in k_E^H/k_E^D with increasing acidity of the brosylate substrate supports this conclusion. However, the decrease in k_E (Figure 4) with increasing acidity of the substrate strongly indicates that the E2 reaction is not the major reaction path to stable alkene (*vide supra*). The interpretation that seems most reasonable, in the light of the evidence for E2 reaction with acetate anion base, is that the stable alkene is formed by both the solvent-promoted E2 route and the carbocation route. The rate of the former reaction increases with increasing acidity of the substrate but
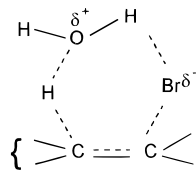
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Scheme 3

does not become the predominant reaction path to stable alkene, even for **3-OBs**. Strong support for this conclusion is obtained from the different sensitivities to substrate acidity as expressed by the Brønsted parameters of $\alpha = -0.10$ for elimination to give stable alkene (k_E) and $\alpha = -0.36$ for reaction to substitution products and terminal alkenes ($k_S + k_T$, Scheme 1 and Figure 4).

Reaction through the ion pair may explain why water shows a slight positive deviation in the Brønsted plot for **3-OBs** (Figure 1). A similar, but more significant deviation, has been found for **1-OTs**.[2] The normal behavior of water as a catalyst is shown in the Brønsted plot for **3-Br** (Figure 1). The catalytic constant for water as a base falls below the Brønsted line for the substituted acetate anions by a factor of 8. Similar deviations were observed for the E2 reaction of **1-I** and **1-Br**.[2] Dehydronation of carbocation intermediates shows similar behavior.[9,11,12] Negative deviations of the catalytic constant for water are well-known for hydron transfer to and from carbon in which H_2O and HO^- are the hydron donor and acceptor, respectively.[13] The low catalytic activity of water as a hydron acceptor in E2 reactions probably reflects some kind of solvation effect. However, the absence of a negative charge is favorable in the E2 transition state because there is an unfavorable electrostatic interaction between a negatively charged base and the developing partial negative charge on the β-carbon.

Stereochemistry of the Elimination Reactions. The two diastereomers **2a-X** and **2b-X** provide very similar results. They both exhibit high, but not exclusive, *anti* stereospecificity with hydroxide and acetate anions (Table 3). The iodides also show high stereospecificity, about 90% *anti* elimination with water as base, but the bromides give only 75% *anti* elimination. A possible explanation is that the transition state of the *syn* elimination is stabilized by hydrogen bonding to the hydronabstracting water molecule, as shown in Scheme 3. This stereochemical route is expected to be less important for the larger and less electronegative iodide ion.

The very similar stereochemical results and the very similar reaction rates of the two diastereomers **2a-X** and **2b-X** show that the bromo substituent has an insignificant steric effect on the elimination reaction. Moreover, the two alkene isomers **5a** and **5b** should have about the same thermodynamic stability.

The chloride **2a-Cl** reacts very slowly with solvent and only the stereochemistry with added bases has been studied. The large amount of *syn* elimination occuring with hexamethylenetetramine (HMTA, $pK_a = 5.13$[14] in water) in methanol might reflect an irreversible E1cB mechanism involving a hydrogenbonded carbanion intermediate. This a mechanism has been proposed for the corresponding elimination from (*R,S*)- and (*R,R*)-1-(1-chloroethyl)indene.[3,15] It is favored by the lower polarity of methanol. Water-promoted hydron abstraction from

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the corresponding *R,S* bromide yields 85% *anti* elimination.[3] This reaction has been proposed to be of E2 type.

Reactions through Ion Pairs. Results that strongly support a carbocationic reaction path for **1-X** have been reported recently.[2] Similar results are obtained with the closely related but more acidic substrates of the present study. Thus, reaction with the acetonitrile component of the solvent to give the amide products and the formation of the terminal alkenes **4** (Scheme 1) strongly indicate carbocation mechanisms (Scheme 2). Moreover, the reaction rate constants ($k_S + k_T$) for the formation of the substitution products with the solvent and formation of the terminal alkene decrease in the order **2a-OBs** > **2a-Br** $\approx$ **2a-I**, **2b-OBs** > **2b-Br** $\approx$ **2b-I**, and **5-OBs** > **5-Br**, consistent with reactions though carbocation intermediates.

There is a gradual decrease in $k_S + k_T$ with increasing acidity of the substrate (Table 1 and Figure 4). This a decrease is expected for carbocationic reactions, since an enhanced acidity decreases the stability of the carbocation-like transition state of the ionization step. Further support for stepwise reaction mechanisms is the predominant retention which is observed with the nucleophilic reactions of the diastereomers **2a-X** and **2b-X** with solvent (Table 4).

How stable are the ion pairs? A very rough estimate of the reactivity of the unsubstituted carbocation intermediate formed from **1-X** is a rate constant for reaction to substitution and elimination products of about 1×10^{12} s^{-1}.[2] This indicates that the substitution reactions with added strong nucleophiles occur through stepwise preassociation mechanisms or, as will be discussed below, through one-step S$_N$2 reactions.

The selectivity of the short-lived carbocation intermediate toward different nucleophiles should be very low. The corresponding unsubstituted tertiary chloride and bromide show selectivities of $k_{N_3}/k_{HOH} = 4-5$ and $k_{MeOH}/k_{HOH} = 0.6-0.7$ (ratios of second-order rate constants).[9] The selectivity ratio k_{MeOH}/k_{HOH} for **1-X** is approximately constant ($\sim$1) at different compositions of methanol–water mixtures.[2] However, there is a small increase in the series OBs $\approx$ OTs < Br < I (Table 5). This change in selectivity might be due to a contribution from S$_N$2 reaction with the methanol component of the solvent. Consistently, there is an increase in the k_{MeOH}/k_{HOH} ratio from about 1 for **1-OBs**, **2a-OBs**, and **2b-OBs** to 1.5 for **3-OBs** (Table 5).

Relatively large fractions of the substitution products with solvent consist of the amides. The measured nucleophilic selectivity is $k_{MeCN}/k_{HOH} = 0.4-0.5$ in solvent mixtures with lower acetonitrile content but decreases at higher concentrations (Table 5). The k_{MeCN}/k_{HOH} ratio is larger with the secondary substrates than with the analogous tertiary derivatives 9-(2-X-2-propyl)fluorene,[16] consistent with the expected higher reactivity and lower selectivity of the former.

More stable carbocations do not react with acetonitrile under neutral conditions. We have suggested that the unexpectedly high reactivity of acetonitrile reflects the high dipole moment of acetonitrile (11.8 compared to 5.9 for water). Accordingly, charge–dipole interactions between the carbocation and acetonitrile are assumed to be of importance in stabilizing the ion–molecule pair.[16]

Bimolecular Substitution Reactions (S$_N$2). Efficient nucleophiles give bimolecular substitution reactions with all of the studied substrates. Second-order reactions of **1-X** are progressively more important for the leaving groups BsO$^-$ $\approx$ TsO$^-$ < Cl$^-$ < Br$^-$ < I$^-$.[2] Thus, for **1-OBs** with 0.75 M SCN$^-$, only about 20% of the substitution products consist of **1-SCN** and **1-NCS**, but the corresponding fraction for **1-I-*d*** is about 80%.[2] This is an example of "synergism" between leaving

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group and nucleophile which has been seen previously in nucleophilic displacement reactions.[17] It is likely caused by a favorable interaction between polarizable entering and leaving groups in the "coupled" S_N2 transition state.

The large assistance provided by efficient nucleophiles is in strong contrast to the anomalously small nucleophilic discriminations which were observed for the corresponding tertiary substrates. For example, the tertiary bromide reacts to give substitution products only about three times more rapidly with a thiocyanate anion than with a solvent water molecule.[10] The reactions of the tertiary substrates, owing to the very short lifetime of the ion-pair intermediate, occur through stepwise preassociation mechanisms.

Thiocyanate ion, owing to its ambident character, gives rise to two products (Table 5). There is a change in reactivity of the S and N parts of the nucleophile with a change in the leaving group of the substrate. The more polarizable ("soft") the leaving group is the more of **1-SCN** relative to **1-NCS** is formed. This is in accord with the concept of synergism between leaving group and nucleophile which reflects favorable interaction between polarizable entering and leaving groups in the coupled, concerted transition state, since sulfur is more easily polarized than nitrogen. Consistently, the Grunwald–Winstein parameter m_{NCS} is significantly greater than m_{SCN} for reaction of **1-OBs**, which shows that the transition state with the N atom as nucleophile is more polar than the transition state with the S atom.[2] Moreover, there is a gradual increase in the reactivity of S relative to N of thiocyanate in the order **1-OBs** < **2a-OBs** ≈ **2b-OBs** < **3-OBs** (Table 5).

An explanation is that the isocyanate product comes from reaction through a stepwise preassociation carbocation mechanism but the thiocyanate originates from a coupled concerted reaction. Another possibility is that both products are formed by S_N2 reactions but that there is a gradual change in the positive charge on the central carbon atom. The fact that only 77–78% inversion is observed with **2a-OBs** and **2b-OBs** supports the first alternative. The nucleophilic selectivity k_{SCN}/k_{HOH} with thiocyanate anion shows the same trend as the thiocyanate–isocyanate product ratio from 16 with **1-OBs** to 122 with **3-OBs** (Table 5).

The reactions with water in aqueous acetonitrile and aqueous methanol show a surprisingly large amount of retention, about 90% (Table 4). A reasonable explanation is that π-orbitals of the fluorenyl moiety assist the ionization by interaction with the developing p-orbital on the backside of the reaction center. Theoretical calculations by MNDO methods support this conclusion.[18] Thus, it has been reported that the fluorenylmethyl carbocation is stabilized significantly by such interactions. The somewhat smaller amount of retention with methanol as nucleophile may indicate some contribution from an S_N2 reaction route.

Experimental Section

General Procedures. NMR spectra were recorded with a Varian XL 300 or a Unity 400 spectrometer for ^{1}H at 300 MHz and 400 MHz, for ^{13}C at 75.4 MHz and 100.6 MHz, at 25 °C unless stated otherwise. Chemical shifts are indirectly referenced to TMS via the solvent signal (chloroform-d_1 7.26 and 77.00 ppm; DMSO-d_6 2.49 and 39.5 ppm). NMR signals were assigned from P.E.COSY,[19] HSQC,[20] HSBC,[21] and NOE difference spectra.[22]

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The high-performance liquid chromatography analyses were carried out with a Hewlett-Packard 1090 liquid chromatograph equipped with a diode-array detector on a C_{18} (5 μm, 3 × 100 mm) reversed-phase column. The mobile phase was a solution of acetonitrile in water. The reactions were studied at constant temperature in a HETO 01 PT 623 thermostat bath. The pH was measured using a Radiometer PHM82 pH meter with an Ingold micro glass electrode.

The GC analyses were carried out with a Varian 3400 capillary gas chromatograph equipped with a flame ionization detector. Nitrogen was used as the carrier gas. The column was a fused-silica capillary column (Rescom, SE54, 25 m, 250 μm). The injection temperature was 250 °C, and the column temperature was maintained constant at 200 °C.

Materials. Merck silica gel 60 (240–400 mesh) was used for flash chromatography. Diethyl ether and tetrahydrofuran were distilled under nitrogen from sodium and benzophenone. Pyridine and methylene chloride were distilled under nitrogen from calcium hydride. 2-Bromofluorene was purchased from Lancaster and used without further purification. Methanol and acetonitrile were of HPLC grade. All other chemicals were of reagent grade and used without further purification. The deuterium content of all the deuteriated compounds was measured by ^{1}H NMR to be >99.5 atom % [2]H in the 9-position of the fluorene moiety. The deuteriated compounds 2-bromo-(9-^{2}H)-9-(1-X-ethyl)-fluorene and 2,7-dibromo-(9-^{2}H)-9-(1-X-ethyl)fluorene (X = OH, Br, I, OBs) were synthesized using the same methods as used for the corresponding nondeuteriated analogs.

2-Bromo-(9,9-[2]H$_2$)-fluorene and **2,7-Dibromo-(9,9-[2]H$_2$)-fluorene** were prepared by the same method as has been used for synthesis of (9,9-[2]H$_2$)-fluorene.[2,23]

(R,R)- and (R,S)-2-Bromo-9-(1-hydroxyethyl)fluorene (2a-OH) and (2b-OH). A solution of butyllithium (12.8 mL of a 1.6 M solution in hexane, diluted with 30 mL of dry ether) was added to 2-bromofluorene (5 g), dissolved in dry ether (100 mL), at <−50 °C. After the mixture was stirred at this temperature for 1.5 h, freshly distilled acetaldehyde (30 mL) was added slowly with stirring. After addition, the mixture was stirred for another 10 min. The reaction mixture was poured into a mixture of ice and 2 M hydrochloric acid. The mixture was extracted with ether three times. The combined ether fractions were washed with water to neutrality, followed by washing with brine. Recrystallization from pentane–ether and pentane–dichloromethane gave pure diastereomer **2a-OH**: mp 138–139 °C.

The mother liquid was recrystallized further to give a mixture of the two diastereomers. These were separated with flash chromatography on silica gel with hexane–ethyl acetate–dichloromethane (9:1:2) as eluent. The end fractions contained pure **2b-OH**: mp 107–108 °C.

(R,R)-2-Bromo-9-(1-bromoethyl)fluorene (2a-Br) was prepared by treatment of the alcohol **2a-OH** with ZnBr$_2$–HBr in chloroform according to the method described before.[4] The reaction was followed by HPLC. Recrystallization from methanol and hexane gave a product with >99% diastereomeric purity. No other impurities were detected: mp 97–99 °C. The same method was used to prepare (R,S)-2-Bromo-9-(1-bromoethyl)fluorene (**2b-Br**) from **2b-OH**: >98% diastereomeric purity; mp 83–84 °C.

(R,R)-2-Bromo-9-(1-chloroethyl)fluorene (2a-Cl) was prepared from the alcohol **2a-OH** by reaction with ZnCl$_2$–HCl in chloroform as above. Isolation and recrystallization gave a product with >98% diastereomeric purity: mp 73–74 °C. The same method was used to prepare (R,S)-2-Bromo-9-(1-chloroethyl)fluorene (**2b-Cl**) from **2b-OH**: >96% diastereomeric purity; mp 87–88 °C.

(R,R)-2-Bromo-9-(1-iodoethyl)fluorene (2a-I) was prepared from the alcohol **2a-OH** by reaction with ZnI$_2$–HI in chloroform as above. Recrystallization several times from methanol and hexane gave the product with >98% diastereomeric purity: mp 93–95 °C. Similarly, (R,S)-2-Bromo-9-(1-iodoethyl)fluorene (**2b-I**) was prepared from the alcohol **2b-OH**. Recrystallization from hexane–benzene (1:1) gave a product with >98% diastereomeric purity: mp 106–107 °C.

(R,R)-2-Bromo-9-(1-((4′-bromobenzenesulfonyl)oxy)ethyl)-fluorene (2a-OBs) was synthesized by stirring a mixture of **2a-OH**

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(0.25 g), 4-bromobenzenesulfonyl chloride (0.75 g), dry dichloromethane (5 mL), and dry pyridine (2 mL) at room temperature. The reaction was quenched after 3.5 h (about 50% reaction) by addition of 2 M hydrochloric acid. The water phase was extracted twice with dichloromethane. The combined organic phases were washed with water and brine and dried with sodium sulfate. Evaporation of the solvent and separation with flash chromatography on silica gel with 5−20% ethyl acetate−pentane, followed by recrystallization in ethanol−pentane, gave pure **2a-OBs**: mp 149−150 °C. The same method was used to prepare (*R*,*S*)-2-Bromo-9-(1-((4′-bromobenzenesulfonyl)-oxy)ethyl)fluorene (**2b-OBs**) from **2b-OH**: mp 158−159 °C.

(*R*,*R*)-2-Bromo-9-(1-methoxyethyl)fluorene (2a-OMe). Silver oxide was prepared by adding potassium hydroxide (0.15 g) in 3.5 mL of water to a solution of silver nitrate (0.39 g) in 3.5 mL of water.[24] A mixture of the alcohol **2a-OH** (20 mg), iodomethane (5 mL), and the freshly prepared silver oxide was refluxed. After 2 days, no trace of the alcohol was observed by HPLC. (*R*,*S*)-2-Bromo-9-(1-methoxyethyl)fluorene (**2b-OMe**) was prepared from **2b-OH** as described above.

2,7-Dibromofluorene was prepared by bromination of fluorene: mp 166−167 °C (lit.[25] mp 165 °C).

2,7-Dibromo-9-(1-hydroxyethyl)fluorene (3-OH) was prepared from 2,7-dibromofluorene as described above for **2a-OH**: mp 135−136 °C.

2,7-Dibromo-9-(1-bromoethyl)fluorene (3-Br) was prepared by the same method as used for **2a-Br**. Recrystallization from hexane gave pure material: mp 168−169 °C.

2,7-Dibromo-9-(1-iodoethyl)fluorene (3-I) was prepared from the corresponding alcohol by reaction with ZnI_2−HI in chloroform as described above: mp 160−161 °C.

2,7-Dibromo-9-(1-((4′-bromobenzenesulfonyl)oxy)ethyl)-fluorene (3-OBs) was synthesized by the same method as described above for **2a-OBs**. Flash chromatography on silica gel with 5% ethyl acetate−pentane followed by recrystallization from ethanol−pentane gave pure material: mp 169−170 °C.

2,7-Dibromo-9-ethylidenefluorene was synthesized by dissolving 2,7-dibromo-9-(1-bromoethyl)fluorene (**3-Br**) in a mixture of pyridine and dichloromethane. The reaction was quenched with 2 M hydrochloric acid, followed by washing with water and brine and drying over sodium sulfate. Evaporation of the solvent and recrystallization twice from hexane gave pure alkene: mp 139−140 °C.

The stereochemical assignment of the two alcohols **2a-OH** and **2b-OH** was achieved as follows. For each of the two isomers, a conformational search was performed with molecular modeling using the MM^+ parameter set.[26] The dihedral angle between H-9 and H-10 was varied randomly in this search. The relative populations of the conformers found were estimated from their energies using a Boltzman distribution, and only those with at least 1% population were kept.

According to these calculations, the main conformation for both isomers was the one with the methyl group *trans* to H-9 (69% for *R*,*R* isomer and 75% for *R*,*S* isomer). The second most abundant conformer had the OH group in the *trans* position (*R*,*R* isomer 24%, *R*,*S* isomer 15%). In NOE difference experiments, irradiation of H-10 in one isomer gave NOEs to H-8 and to H-1 of 12% and 1%, respectively. On the basis of the calculated conformer distribution, this was assigned to the *R*,*R* alcohol **2a-OH**. The other isomer gave upon irradiation of H-10 NOEs to H-8 and to H-1 of 2% and 7% and was therefore assigned as the *R*,*S* alcohol **2b-OH**. The measurement of equally large coupling constants between H-9 and H-10 in both isomers (4.5 Hz), as well as between H-10 and C-9a (ca. 12 Hz), lends further support for the conformer geometries as suggested by the calculations.

Kinetics and Product Studies. The reaction solutions were prepared by mixing acetonitrile or methanol with water at room temperature, ca. 22 °C. A few microliters of substrate solution dissolved

in tetrahydrofuran was added. Aliquots of this reaction mixture (∼500 μL) were transferred to several 2 mL HPLC flasks, which were sealed with gas-tight PTFE septa and placed in an aluminum block in the water thermostat bath. The concentration of the substrate in the reaction solution was usually about 0.01−0.1 mM. At appropriate intervals, samples were removed and analyzed using the HPLC apparatus. The rate constants for the disappearance of the the substrates were calculated from plots of substrate peak area versus time by means of a nonlinear regression computer program. Very good pseudo-first-order behavior was seen for all of the reactions studied. The separate rate constants for the elimination and substitution reactions were calculated by combination of product composition data obtained from the peak areas, GC analysis, and the relative response factors determined in separate experiments, with the observed rate constants.

Elimination Product Composition Studies. When HPLC analysis showed that the reaction was nearly complete ($t > 6t_{1/2}$), 1,1,1-trichloroethane (500 μL) was added to the reaction mixture (500 μL) in a 2 mL HPLC flask. After shaking vigorously, the mixture was centrifuged. The organic phase was transferred to a pear-shaped flask, and solvent was evaporated with a stream of nitrogen until ∼15 μL were left. Aliquots of this solution were injected directly onto the GC column. The ratio of the two stable alkene stereoisomers **5a** and **5b** was determined from the peak areas. Comparision with ^{1}H NMR analysis showed that the relative response factors were the same within experimental errors.

Determination of Relative HPLC Response Factors. Pure **2a-Br** or **2b-Br** in ethanol was injected on HPLC for at least five times. Then, 500 μL of this solution was transferred to a 2 mL measuring flask and 0.5 M aqueous sodium hydroxide solution (500 μL) was added. After 20 min, 1 M acetic acid (500 μL) was added, the volume adjusted to 2 mL with ethanol, and the sample was analyzed again. The data were used to calculate the relative response factors for the bromides and the stable alkenes **5a** and **5b**.

The relative response factors for **2a-OH**, **2a-Br**, **2b-Br**, and **2b-OH** were calculated from HPLC analysis of a mixture of the two components prepared by weighing. The relative response factors of **3-OH** and 2,7-dibromo-9-ethylidenefluorene were determined in the same way.

Solvolytic Substitution by the Solvent. Product Composition Studies by ^{1}H NMR. Substrate (∼10 mg) was dissolved in a mixture of 200 mL of 40 vol % acetonitrile in water (or 200 mL of 60 vol % methanol in water) and 200 μL of 1 M perchloric acid. After about 95% reaction was reached at 90 °C, the reaction mixture was cooled to room temperature and extracted with chloroform three times. The combined chloroform phases were washed with water and brine and dried over sodium sulfate. The solvent was then removed, and the residue was analyzed by ^{1}H NMR (chloroform-d_1). The diastereomeric ratio of the alcohol was determined by comparing the methyl signals (δ 0.86, 0.93) or the methine signals (δ 4.59, 4.51). The diastereomeric ratio of the two ether products **2a-OMe** and **2b-OMe** for solvolysis of **2a-X** and **2b-X** was measured in a similar way by comparing the ^{1}H NMR signals of the methyl protons (δ 0.58, 0.62).

Substitution by Sodium Thiocyanate. Product Composition Studies by ^{1}H NMR. Substrate (∼10 mg) was dissolved in a mixture of 40 vol % acetonitrile in water (200 mL) in the presence of 1 M sodium thiocyanate and 200 μL of 1 M perchloric acid. The procedure was as above except that benzene-d_6 was used for the analyses. The diastereomeric ratio of the nucleophilic substitution products **2a-SCN-*d*** and **2b-SCN-*d*** was determined by comparing the methine proton signals (δ 3.39, 3.33 ppm).

Supporting Information Available: NMR data of the compounds (3 pages). See any current masthead page for ordering and Internet access instructions.

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